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Research Article

EFFECT OF MANUFACTURING VARIABLE ON DESIGNING OF EXTENDED RELEASE TABLET OF ETODOLAC USING KOLLIDON® SR

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ABSTRACT

Background: The drug Etodolac, is a non-steroidal anti-inflammatory drugs (NSAIDs) prominently used for treatment of chronic rheumatism. **Aims:** The objective of the present study to evaluate the effect of manufacturing process variable on designing of extended release tablet of Etodolac using natural polymer. **Materials and Methodology:** Etodolac control release tablets were prepared by direct compression and wet granulation methods using Kollidon® SR (Semi-synthetic polymer) in different ratios (7, 8, 9 and 10 %) as release rate controlling polymers. The granules were evaluated for flow properties by evaluating bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. The tablets were evaluated for drug polymer compatibility study by FTIR, diameter, weight variation test, hardness, friability, disintegration test, *in vitro* drug release, release kinetics and stability studies. **Results and Discussions:** The FTIR study revealed that no such interactions being taking place in between drug and polymers. The flow property of granules of all tablet batches was found to be good. All the tablet formulations had good tablet physiochemical properties. All Etodolac extended release tablet formulations showed satisfactory drug content and *in vitro* release. **Conclusion:** The results of *in vitro* study, it was concluded that Etodolac matrix tablet containing Kollidon® SR (10.0 %) prepared by wet granulation method, provided most controlled release of water-soluble Etodolac over extended period of time. Thus wet granulation method is the optimized method in designing of extended release tablet of Etodolac.

Keywords: Extended release, NSAIDS, Etodolac, Kollidon® SR, wet granulation.

INTRODUCTION

Numerous techniques were reported previously for preparation of sustained release pharmaceutical formulations such as coating an osmotically active drug core with a semi-permeable membrane, encapsulation of beads, pellets or tablets with different levels and types of diffusion barriers. However use of sophisticated equipments in their formulation, number of critical manufacturing process variables, difficulties in scale-up and use of skilled manpower had limited their routine use in the industry. A common technique of preparation of sustained release tablets include the use of a matrix or carrier-based system, in which the active ingredient is dispersed uniformly throughout a controlled release functional polymer[1-3].

Etodolac, 2-(1,8-diethyl-4,9-dihydro-3H-pyrano[3,4-b]indole-1-il)acetic acid is an example of non-steroidal anti-inflammatory drugs (NSAIDs). It is especially beneficial in treatment of chronic conditions of arthritis, osteoarthritis and similar rheumatismal diseases. Etodolac is a medicine with a short elimination half life of 8 h and low and pH-dependent solubility between pH 3 to 7[4-6]. Thus in order to maintain the effective plasma levels of the drug, its frequent administration are needed which would in turn lead to NSAID-

related side effects on gastro-intestinal (GI) system. Also once-a-day sustained action medications for drug molecules with short half lives typically like Etodolac present formulation problems because of their relatively short residence time into GI tract before elimination[7-9].

Thus the present study aimed to evaluate the **e**ffect of manufacturing process variable on designing of extended release tablet of Etodolac using natural polymer.

MATERIALS AND METHODOLOGY

MATERIALS

Etodolac was obtained as gift sample from Platico Pharma (Indore, India). Polyvinyl acetate containing polyvinylpyrrolidone was supplied as a gift sample by BASF Corporation (Washington, USA) as Kollidon®SR. All other commonly used excipients with reported compatibility with Etodolac and chemicals were of analytical grade and procured from authorized supplier.

Formulation design and preparation of Etodolac matrix tablets

Etodolac extended release tablets 400 mg were prepared by both direct compression (Formulations F1, F2, F3 and F4) and wet granulation (Formulations F5, F6, F7 and F8) techniques by using natural polymer, Kollidon® SR at concentrations of 7, 8, 9 and 10 % w/w. Anhydrous lactose, talc (2 % w/w) and magnesium stearate (2 % w/w) were used as diluent, glidant and lubricant respectively. The PVP K-30 and isopropyl alcohol used in wet granulation method were used as binder and co-solvent. The wet granulation was done by using sieve No. 16. The granules were dried in hot air oven at 45°C for 30 min and air dried granules were kept for two days. For all batches, the drugs were mixed with excipients in a Turbula apparatus (WA Bachofen, Basel, Switzerland) for 10 min at 30 rpm, and compressed between 7 mm round flat faced punches on a ten stations automatic punching machine (Cad Mack Ltd. Mumbai, India)[10].

CHARACTERIZATION

Evaluation of Etodolac and Kollidon® SR granules

Angle of repose, Carr's index, Bulk density and Hausner's ratio were determined to assess the flow ability of the prepared Etodolac granules[11-14].

Angle of repose

The angle of repose was determined by allowing the granules to fall freely through a fixed funnel at a distance of 1cm above the horizontal surface with the apex of the conical pile just touching the tip of the funnel.

The angle of repose (θ) was calculated by the formula:

$$\theta = \tan^{-1}(h/r) \quad \text{..... (1)}$$

Where, h is cone height in cm. of granules and r is radius in cm. of circular base formed by granules on the ground.

Bulk density

The product was tapped using bulk density apparatus (Terknik P-87, India) for 1000 taps in a cylinder and the change in volume were measured. The Carr's index and Hausner's ratio were calculated by formula:

Carr's index (%) =

$$[(D_f - D_o) / D_f] \times 100 \quad \text{..... (2)}$$

Hausner's ratio =

$$D_f / D_o \quad \text{..... (3)}$$

Where, D_o is the poured density in g/cc and D_f is the tapped density in g/cc.

Quality control test on the Etodolac matrix tablets

Hardness

Hardness study was conducted by following the guidelines of the USP. Six tablets were taken and hardness of each tablet of each batch was measured by Pfizer type Hardness Tester (Campbell Electronics Company, Mumbai, India)[15].

Diameter

The study of the tablet thickness was conducted by the following USP guidelines. For these fifteen tablets were taken for each batch and thickness were measured by using Digimatic caliper, Mitutoyo Corporation, Japan[15].

Friability

Friability testing was done by using 6 tablets for each batch by using Friability Test Apparatus (Campbell Electronics, Mumbai, India)[15].

Weight variation

Weight variation study was conducted by following guidelines of USP. In short 20 tablets were taken and they were weighed together and individually in electronically digital balance. The individual weight variations were studied from the mean weight of each set[15].

Drug content

About 20 tablets were selected randomly from

each formulation, weighed. The weighed tablets were powdered. The powder equivalent to 100 mg of Etodolac was accurately weighed and dissolved in phosphate buffer pH 6.8. After suitable dilution, the solution was analyzed for drug content by using UV-Visible spectrophotometer (Shimadzu UV 1700, Japan) at 276 nm[16].

In vitro release study

Dissolution rate of Etodolac and its release from all the tablet formulations was performed, in triplicate using U.S.P. grade XXXII, Type II Dissolution Test Apparatus (Electrolab, Model: TDT-06P, India). Samples were placed in the dissolution vessels containing 900 mL of Phosphate buffer (pH 6.8) solutions maintained at 37.0±0.5°C and stirred at 50 r.p.m. +/- 4%. Selection of Phosphate buffer, pH 6.8 as dissolution medium signifies simulation of intestinal condition in terms of pH where the extended release formulation is expected to release the drug. The aliquots of suitable volume (i.e. 5 mL) were collected at predetermined intervals of time and replaced immediately with equal volumes of fresh dissolution medium, maintained at the same temperature. After filtration, each of the collected aliquots was suitably diluted with methanol and analyzed spectrophotometrically at λ_{max} of 276 nm. The data was studied using PCP-Disso v2.08 software[16].

Drug release kinetics

In order to determine mechanism of drug release from the tablet formulations, the drug release data were outfitted into various drug releases mathematical kinetics equations such as zero order, first order models, Higuchi model, Hixon–Crowell Square root and Korsmeyer-Peppas model, which were based on equations that describe the drug release phenomenon[17-19].

Stability study

Stability study was conducted on optimized formulation of Etodolac matrix tablet at storage conditions like temperature 40±2 °C and humidity 75±5 % RH as per ICH guidelines, to assess the changes in their molecular interactions, assay and drug release during their storage in Alu-Alu blister packs over the period 6 months[20,21].

Drug-excipient compatibility study

Drug-excipient compatibility screening to identify drug – excipient interactions and to avoid potential stability problems was performed by preparing the physical mixtures of Etodolac with each of Kollidon® SR in a ratio of 1:10 and filled into the Glass-I amber colored vials of suitable size. The compatibility was assessed at the end of 1 month by observing the changes in color, appearance and confirmed with the help of Fourier Transform Infrared (FT-IR) spectroscopy using Tensor-27 Spectrometer (Bruker Optik GmbH, Germany) operated with Star^e software (version 9.01). In FT-IR, about 2–3 mg of the samples was finely ground with dry KBr and mounted on the sample cell. The spectra were scanned over wave number range of 4,000−450 cm^{-1} [22].

RESULTS AND DISCUSSION

The direct compression and wet granulation methods with formulation additive were found to be efficient for successful preparation of Etodolac tablets (Table 1). The prepared granules were evaluated flow properties by measurement of angle of repose and the result are given in Table 2. The bulk density was found in the range of 0.196±0.0001 to 0.336±0.0006 g/cc. The tapped density was found in the range of 0.225±0.0011 to 0.440±0.0029 g/cc. The bulkiness was found between 2.976±0.0054 to 5.095±0.0037 cc/g, demonstrating good flow property. The granules of all tablet formulations had Hausner's ratio of 1.316±0.0068 or less (less than 1.5) indicating good flowability. The Carr's index was found between 12.34±0.4145 to 24.01±0.3921 %, demonstrating good flow property. The good flowability of the granules was also evidenced with angle of repose within range of 28.22±0.2783 to 31.90±0.6211º, which is below and almost equal to 30° indicating good flowability. The diameter (12.52±0.0632 to 12.56±0.0516 mm) of all tablet formulations was almost same (Table 3). The hardness of all tablet formulations was ranges from 5.85±0.3028 to 6.15±0.2635 kg/cm^2. Hardness of tablet formulations increased with increase in concentration of Kollidon® SR. The hardness of all extended release tablet formulations was within Pharmacopeial limit. All the batches of tablet exhibited equal uniformity in weight (598.1±3.9772 to 601.0±6.1044 mg). The friability of all tablet formulation was ranges from 0.272±0.0996 to 0.834±0.0718 %. All tablet formulations passed friability test as per Pharmacopoeial limits of USP-2002, as percentage loss on friability was less than 1 %. All the batches of tablet exhibited good uniformity in drug content (98.011±0.5360 to 99.73±0.0675 %). The maximum drug content (99.73±0.0675 %) was achieved with tablet formulation F8 using 10 % of Kollidon® SR as release rate controlling polymer. Almost all the tablet formulations were able to extend the drug release. Almost all the tablet formulations were

able to suitably extend the drug release from their dosage form. *In vitro* dissolution study showed (Table 4) that drug released from the tablet formulations, prepared by using Kollidon® SR employing direct compression and wet granulation methods at four different concentrations was more than 70 % in 840 min (Fig 1). Almost all the tablet formulations were able to extend the drug release more efficiently. The Etodolac tablet formulations F3, F4, F7 and F8 released drug up to more extended time. The tablet formulation F1 showed lesser drug release profile that release drug up to lesser extended period of time (88.37±0.3953 in 480 min). Among all the tablet formulations, the tablet formulation F8 (Containing 10 % of Kollidon® SR prepared by wet granulation method) released drug (71.67±0.567 % in 840 min) in more controlled manner over extended period of time. Model dependant methods were used to investigate the kinetics of drug release from the formulations. *In vitro* drug release kinetic study reveled that (Table 5) Etodolac tablet formulations F8 released drug with zero order kinetics, where as tablet formulations F5 and F6 release drug following Hixon-Crowell model. The tablet formulation F2, F3 and F4 released drug with Higuchi release kinetic. The tablet formulation F1 and F7 released drug with Korsmeyer-Peppas kinetic. From the Korsmeyer-Peppas model, it is reveled that the drug release profile tablets formulations F1 to F8 follows non-Fickian transport mechanism.

Unchanged position of the characteristic absorption bands with respect to Etodolac, Kollidon® SR in the FT-IR spectrum of the blend of Etodolac and Kollidon® SR mixture suggested compatibility of the functional polymers with the drug (Fig 2). Also the absorption bands at 3342 cm^{-1} corresponding to secondary N-H stretching and at 1738 cm^{-1} corresponding to C=O stretching with respect to Etodolac was not found to be broadened or shifted to lower wave number, which indicated absence of intermolecular hydrogen bonding between the drug and the functional polymer molecules in the blend. The FTIR study reveled that no such physical and chemical interaction being taking place in between Etodolac and Kollidon® SR[23,24].

The tablet formulation F8 containing 10 % w/v of Kollidon® SR prepared by wet granulation method, as drug release controlling polymer, was the optimized tablet formulation as it showed satisfactory hardness, drug content and drug release profile (in more controlled manner over extended period of time) with zero order release kinetic. The stability study of optimized tablet formulation (F8) was carried out at temperature 40±2 °C and humidity 75±5 % RH as per ICH guidelines. The tablets were found to be stable at such conditions; other parameters were found to be unaffected and were under Pharmacopoeial limits of USP.

CONCLUSION

From the above experimental study it could be concluded that the tablet formulation F8 containing 10 % w/v of Kollidon® SR (as drug release controlling polymer) was the optimized tablet formulation as it showed satisfactory drug release profile (in more controlled manner over extended period of time) with zero order release kinetic. Thus wet granulation method as process variable was found to more efficient than direct compression method for designing of extended release tablet formulation of NSAID drug that is Etodolac.

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Table 1: The matrix tablet formulations of Etodolac with manufactured by direct compression and wet granulation methods

Ingredients (mg)	Concentration (in percent of tablet weight) of a functional polymer							
	7%	8%	9%	10%	7%	8%	9%	10%
	Direct compression				Wet granulation			
	F1	F2	F3	F4	F5	F6	F7	F8
Etodolac	400	400	400	400	400	400	400	400
Kollidon® SR	42	48	54	60	42	48	54	60
Lactose anhydrous	134	128	122	116	122	116	110	104
PVP K-30	-	-	-	-	12	12	12	12
Isopropyl alcohol	-	-	-	-	q.s.	q.s.	q.s.	q.s.
Talc	12	12	12	12	12	12	12	12
Magnesium Stearate	12	12	12	12	12	12	12	12
Total weight	600	600	600	600	600	600	600	600

q.s. – Quantity sufficient

Table 2: Pre compression parameters of extended release formulation prepared by direct compression and wet granulation methods for Etodolac with Kollidon® SR

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Bulk density (g/cc)(n=5) (X±SEM)	0.333± 0.0014	0.334± 0.0027	0.334± 0.0015	0.336± 0.0006	0.197± 0.0008	0.196± 0.0001	0.196± 0.0001	0.197± 0.0006
Tapped density (g/cc)(n=5) (X±SEM)	0.4360± 0.0007	0.439± 0.0013	0.437± 0.0013	0.440± 0.0029	0.228± 0.0028	0.225± 0.0011	0.225± 0.0022	0.225± 0.0017
Bulkiness (cc/g)(n=5) (X±SEM)	2.9978± 0.0126	2.994± 0.0243	2.990± 0.0135	2.976± 0.0054	5.072± 0.0208	5.095± 0.0037	5.080± 0.0032	5.057± 0.0152
Carr's index (%)(n=5) (X±SEM)	23.482± 0.4435	24.01± 0.3921	23.56± 0.4077	23.71± 0.5367	13.68± 0.9236	13.14± 0.5023	12.66± 0.8044	12.34± 0.4145
Hausner's ratio	1.3069± 0.0076	1.316± 0.0068	1.308± 0.0070	1.311± 0.0092	1.158± 0.0124	1.151± 0.0067	1.145± 0.0105	1.140± 0.0054
Angle of repose(θ)(n = 3) (X±SEM)	28.724± 0.5444	29.28± 0.7858	28.93± 0.5607	28.22± 0.2783	31.90± 0.6211	30.98± 0.6799	30.74± 0.5049	29.44± 0.1793

Each data represents mean ± standard error of mean (n = no. of observations).

Table 3: Quality control tests of various Etodolac extended release tablet formulations prepared by direct compression and wet granulation methods

Parameters	Formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
Diameter[a] (mm) (X±SEM)	12.55± 0.0527	12.53± 0.0675	12.54± 0.0516	12.53± 0.0483	12.56± 0.0516	12.52± 0.0632	12.53± 0.0675	12.53± 0.0675
Hardness[a] (kg/cm^2) (X±SEM)	5.85± 0.3028	5.91± 0.3929	5.94± 0.4169	6.04± 0.3062	6.12± 0.2781	6.15± 0.2635	6.11± 0.1792	6.02± 0.2781
Weight[b] (mg) (X±SEM)	598.1± 8.0518	600.35± 6.8386	601.0± 6.1044	599.9± 6.77	599.7± 5.0874	598.1± 3.9772	599.5± 3.9270	599.5± 4.2112
Friability[c] (%)(X±SEM)	0.817± 0.0907	0.801± 0.0151	0.796± 0.0106	0.834± 0.0718	0.355± 0.1229	0.323± 0.1010	0.305± 0.1348	0.272± 0.0996
Drug content[d] (%)(X±SEM)	98.011± 0.5360	98.635± 0.2435	98.557± 0.4107	99.22± 0.3573	99.53± 0.1170	99.34± 0.2701	99.532± 0.3092	99.73± 0.0675

Each data represents mean ± standard error of mean. a – Test done with 10 tablets. b – Test done with 20 tablets. c – Test done with 10 tablets three times. d – Test done with 20 tablets three times

Table 4: Comparison of drug release profile from extended release Formulation prepared by direct compression and wet granulation methods for Etodolac with Kollidon® SR

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
30	3.06± 0.3253	3.04± 0.355	2.52± 0.3020	1.73± 0.158	3.09± 0.2108	2.88± 0.2425	2.16± 0.2107	1.35± 0.1510
90	12.00± 0.3517	10.28± 0.366	8.48± 0.3711	7.88± 0.227	10.91± 0.210	9.64± 0.2400	7.92± 0.2350	7.34± 0.1833
150	20.67± 0.3940	16.79± 0.329	15.48± 0.3889	13.29± 0.221	17.78± 0.210	16.03± 0.210	14.42± 0.237	12.94± 0.124
210	30.06± 0.5074	24.94± 0.360	22.34± 0.4267	20.12± 0.398	25.79± 0.177	23.33± 0.180	19.94± 0.240	18.94± 0.160
270	37.76± 0.4423	31.37± 0.360	29.01± 0.3804	25.45± 0.246	32.94± 0.297	30.32± 0.242	27.90± 0.265	24.03± 0.151
330	45.25± 0.2901	40.11± 0.375	35.91± 0.3940	29.84± 0.539	39.38± 0.205	37.78± 0.210	33.53± 0.302	29.23± 0.175
390	49.52± 0.4477	46.23± 0.601	40.25± 0.9223	36.58± 0.510	46.63± 0.210	44.31± 0.145	39.58± 0.295	35.95± 0.275
450	55.56± 0.4062	51.60± 0.576	47.59± 0.4606	44.11± 0.485	53.91± 0.124	49.60± 0.183	45.71± 0.355	40.61± 0.335
840	88.37± 0.3953	85.14± 0.366	78.81± 0.6627	75.74± 0.735	85.06± 0.710	81.01± 0.866	76.39± 0.860	71.67± 0.567

Each data represents mean ± standard error of mean (n = 3). Each value is expressed as cumulative percentage drug release

Table 5: *In vitro* drug release kinetic data of extended release tablet formulations of Etodolac

Formulations	Correlation Co-efficient (r^2) value				Korsmeyer-Peppas	
	Zero order	First order	Higuchi	Hixson- crowell	R^2	Slope (n)
F1	0.9872	0.9579	0.9793	0.9914	0.9959	1.0288
F2	0.9714	0.9592	0.9929	0.9928	0.9842	1.0283
F3	0.9598	0.9507	0.9942	0.9910	0.9769	0.9474
F4	0.8989	0.9174	0.9867	0.9837	0.9599	0.8688
F5	0.9836	0.9650	0.9811	0.9940	0.9938	1.0213
F6	0.9860	0.9736	0.9790	0.9960	0.9954	1.0396
F7	0.9906	0.9767	0.9733	0.9958	0.9960	1.0925
F8	0.9959	0.9753	0.9675	0.9933	0.9876	1.1794

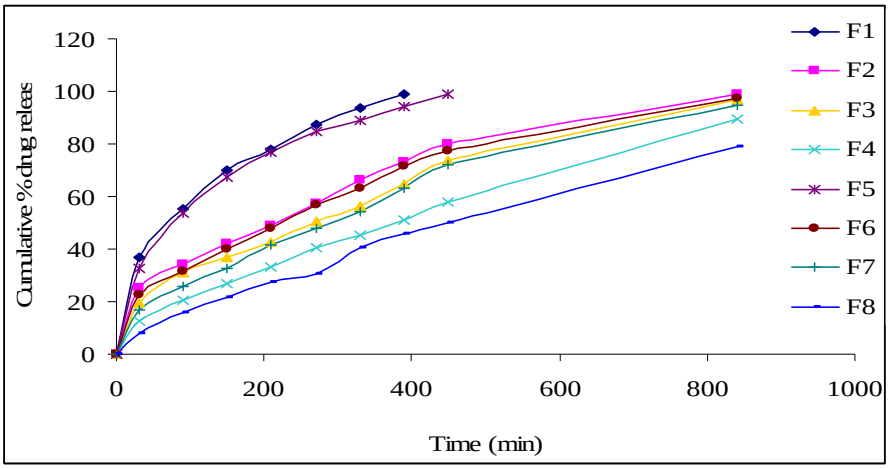
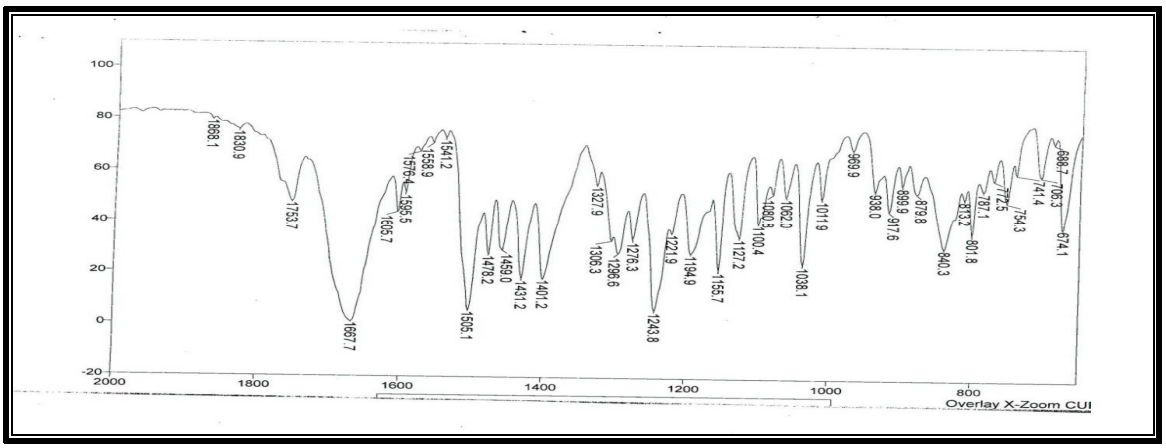


Fig. 1:Drug release profile chart – Extended release formulation prepared by direct compression and wet granulation methods for Etodolac with Kollidon® SR
Each data represents mean ± standard error of mean (n = 3)



(A)

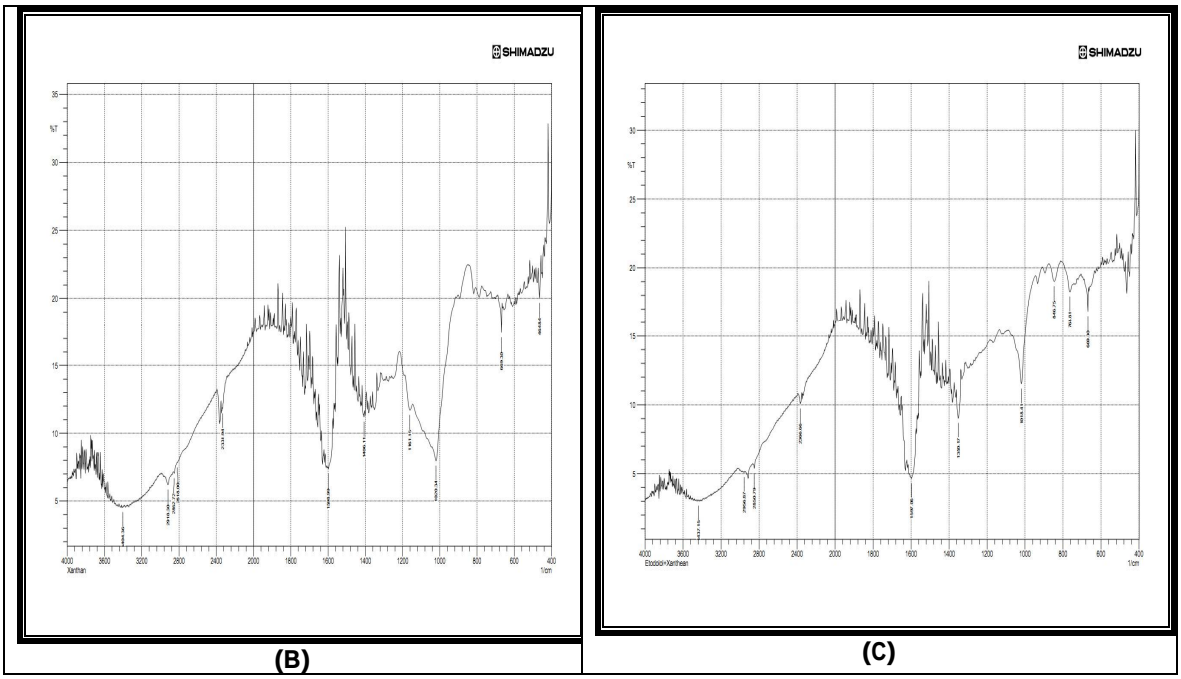


Fig. 2: FTIR spectrum of Etodolac pure drug (A), Kollidon® SR (B) and physical mixture of drug and Kollidon® SR over wave number range of 4,000–450 cm^{-1}

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